LIM homeobox 2 promotes interaction between human iPS-derived hepatic progenitors and iPS-derived hepatic stellate-like cells.

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Public Summary:
Human induced pluripotent stem cells (iPSCs) offer a potential unlimited source of adult cell types with numerous applications in regenerative medicine. However, generating mature and functional cell types from iPSCs is still challenging. Here, we identify genes regulating the generation and maturation of liver cells from iPSCs. These findings may help to generate mature liver cells for drug toxicity studies and ultimately for liver transplantation.

Scientific Abstract:
Human induced pluripotent stem (iPS) cells can differentiate into hepatocyte lineages, although the phenotype of the differentiated cells is immature compared to adult hepatocytes. Improvement of cell-cell interactions between epithelium and mesenchyme is a potential approach to address this phenotype issue. In this study, we developed a model system for improving interactions between human iPS-derived hepatic progenitor cells (iPS-HPCs) and human iPS-derived hepatic stellate cell-like cells (iPS-HSCs). The phenotype of iPS-HSCs, including gene and protein expression profiles and vitamin A storage, resembled that of hepatic stellate cells. Direct co-culture of iPS-HSCs with iPS-HPCs significantly improved hepatocytic maturation in iPS-HPCs, such as their capacity for albumin production. Next, we generated iPS cell lines overexpressing LIM homeobox 2 (LHX2), which suppresses myofibroblastic changes in HSCs in mice. Hepatocytic maturation in iPS-HPCs was significantly increased in direct co-culture with iPS-HSCs overexpressing LHX2, but not in co-culture with a human hepatic stellate cell line (LX-2) overexpressing LHX2. LHX2 regulated the expression of extracellular matrices, such as laminin and collagen, in iPS-HSCs. In conclusion, this study provides an evidence that LHX2 upregulation in iPS-HSCs promotes hepatocytic maturation of iPS-HPCs, and indicates that genetically modified iPS-HSCs will be of value for research into cell-cell interactions.